US 20080004691A1

(19) **United States**

(12) **Patent Application Publication**

Weber et al.

(10) **Pub. No.: US 2008/0004691 A1**

(43) **Pub. Date: Jan. 3, 2008**

(54) **MEDICAL DEVICES WITH SELECTIVE COATING**

(75) Inventors: **Jan Weber**, Maastricht (NL); **Liliana Atanasoska**, Edina, MN (US); **James Lee Shippy**, Maple Grove, MN (US); **Edward E. Parsonage**, St. Paul, MN (US)

Correspondence Address:
FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

(73) Assignee: **BOSTON SCIENTIFIC SCIMED, INC.**, Maple Grove, MN (US)

(21) Appl. No.: **11/763,770**

(22) Filed: **Jun. 15, 2007**

Related U.S. Application Data

(60) Provisional application No. 60/818,101, filed on Jun. 29, 2006.

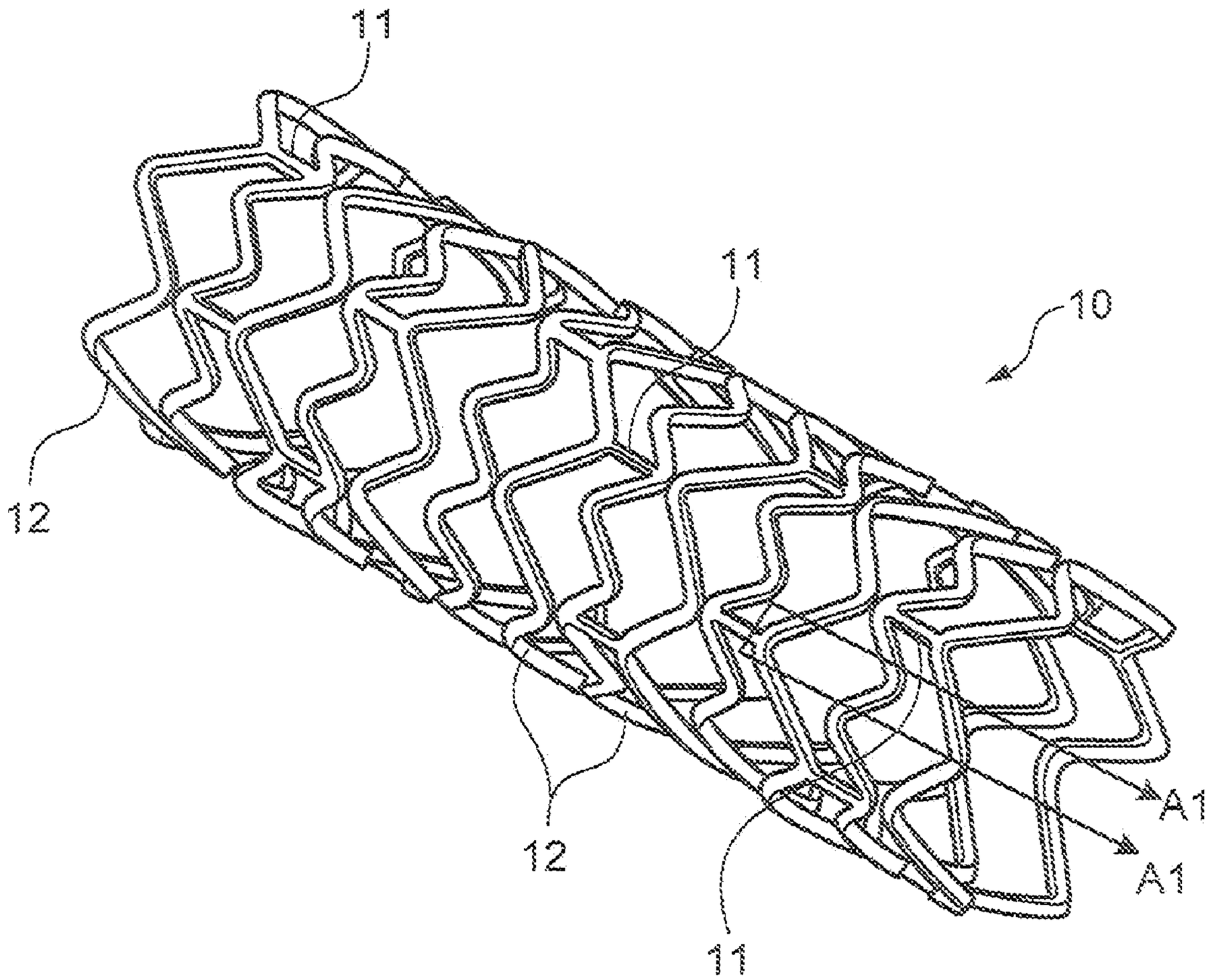
Publication Classification

(51) **Int. Cl.**
A61F 2/06 (2006.01)

(52) **U.S. Cl.** **623/1.16**; 427/2.25

(57) **ABSTRACT**

Medical devices, such as endoprostheses, and methods of making the devices are described. In some embodiments, a medical device includes a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface and an outer abluminal wall surface and defining a central lumen or passageway. The inner luminal wall surface and side wall surface of the bands and connectors forming transverse passageways through the elongated tubular structure can bear a coating of hydrophilic material and the outer abluminal wall surface of the tubular structure can bear a coating of hydrophobic material.



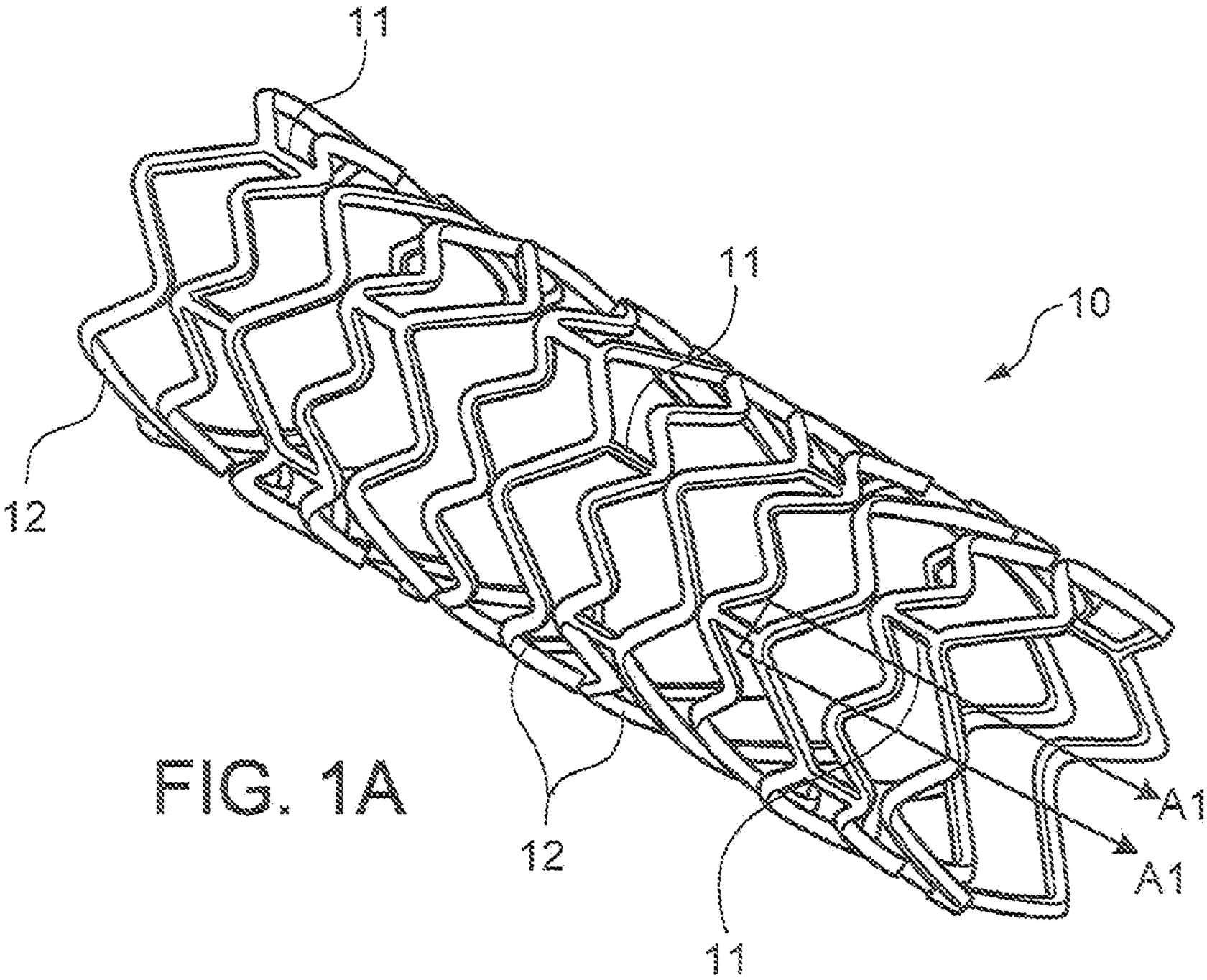


FIG. 1A

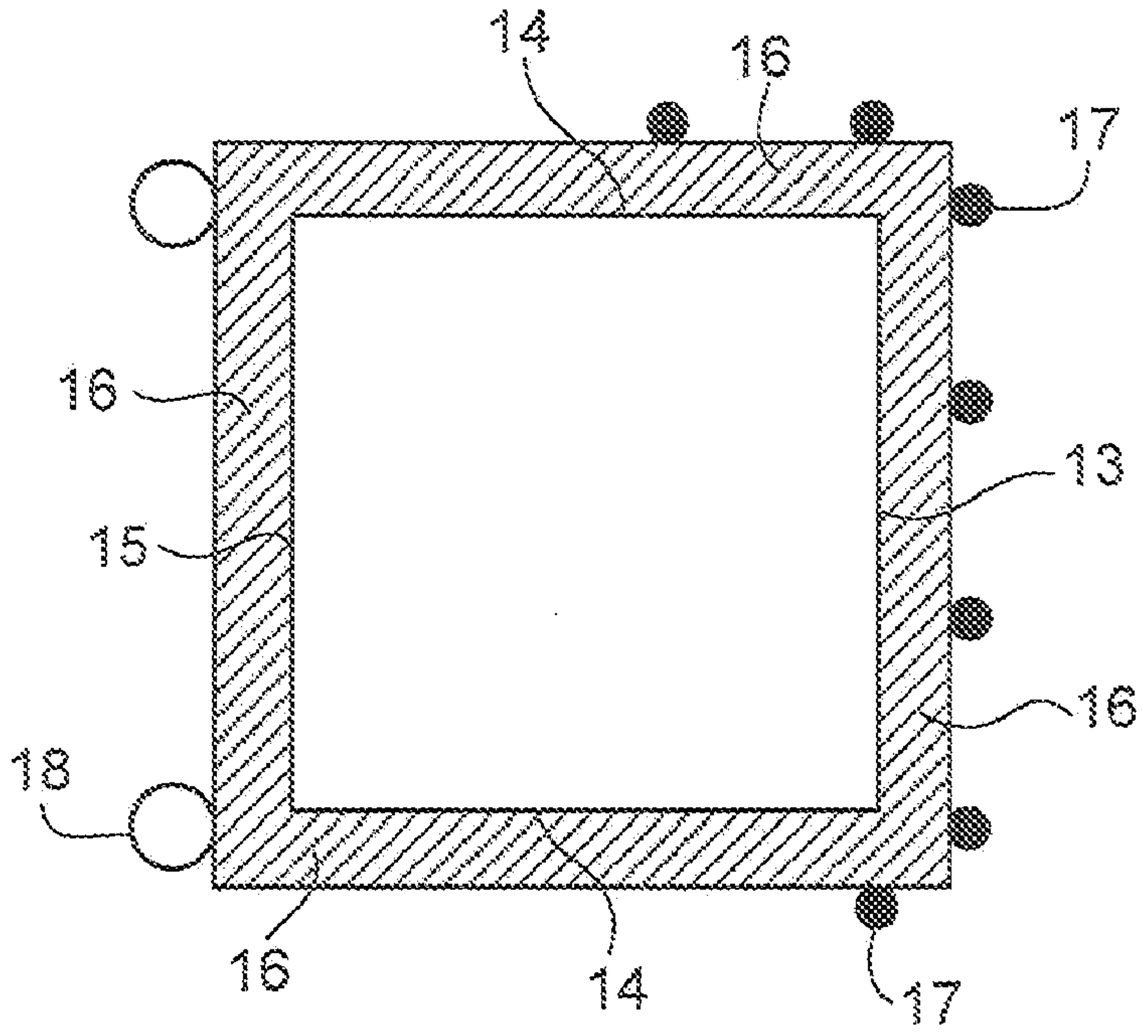


FIG. 1B

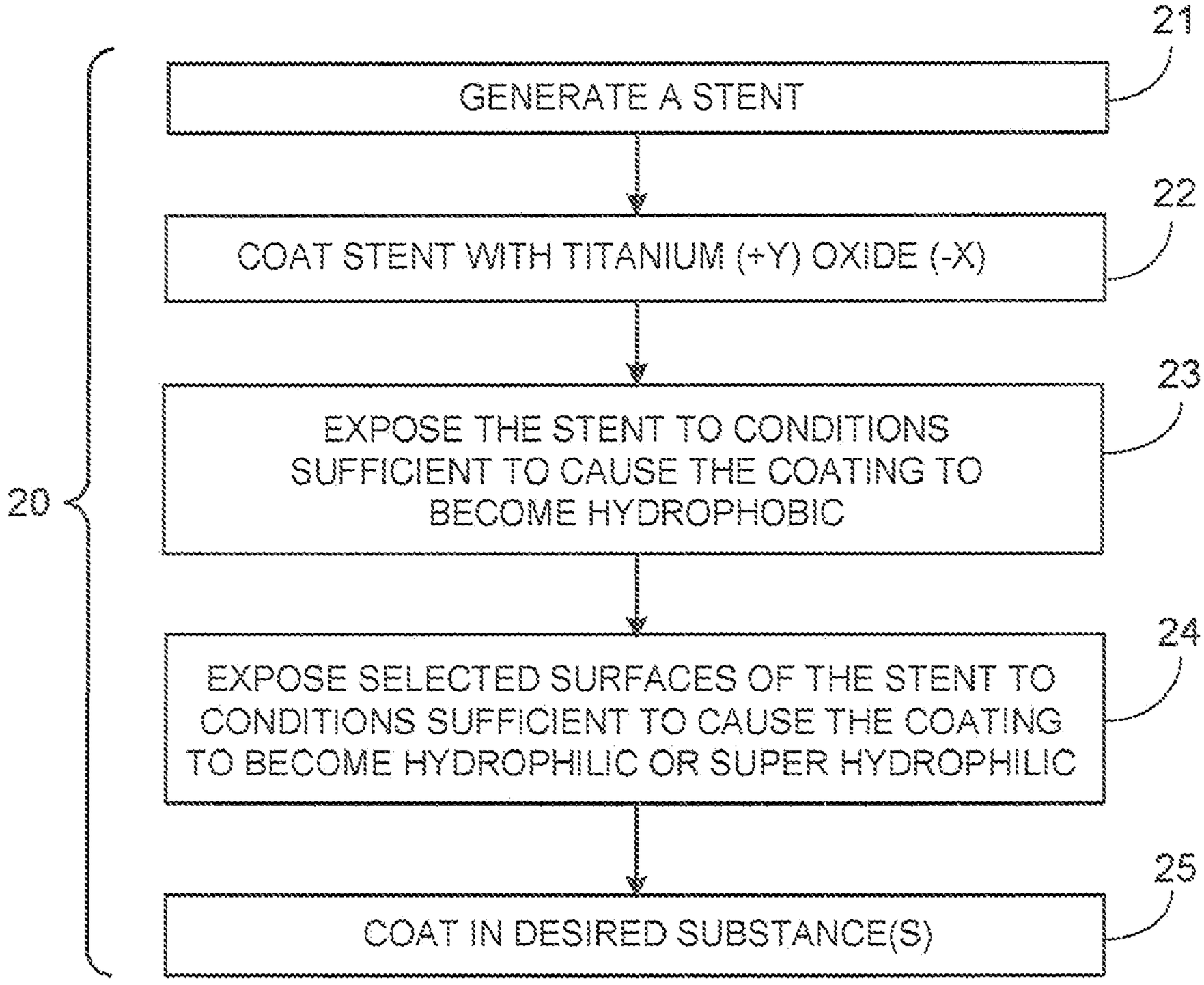

20
21
GENERATE A STENT
22
COAT STENT WITH TITANIUM (+Y) OXIDE (-X)
23
EXPOSE THE STENT TO CONDITIONS SUFFICIENT TO CAUSE THE COATING TO BECOME HYDROPHOBIC
24
EXPOSE SELECTED SURFACES OF THE STENT TO CONDITIONS SUFFICIENT TO CAUSE THE COATING TO BECOME HYDROPHILIC OR SUPER HYDROPHILIC
25
COAT IN DESIRED SUBSTANCE(S)

FIG. 2

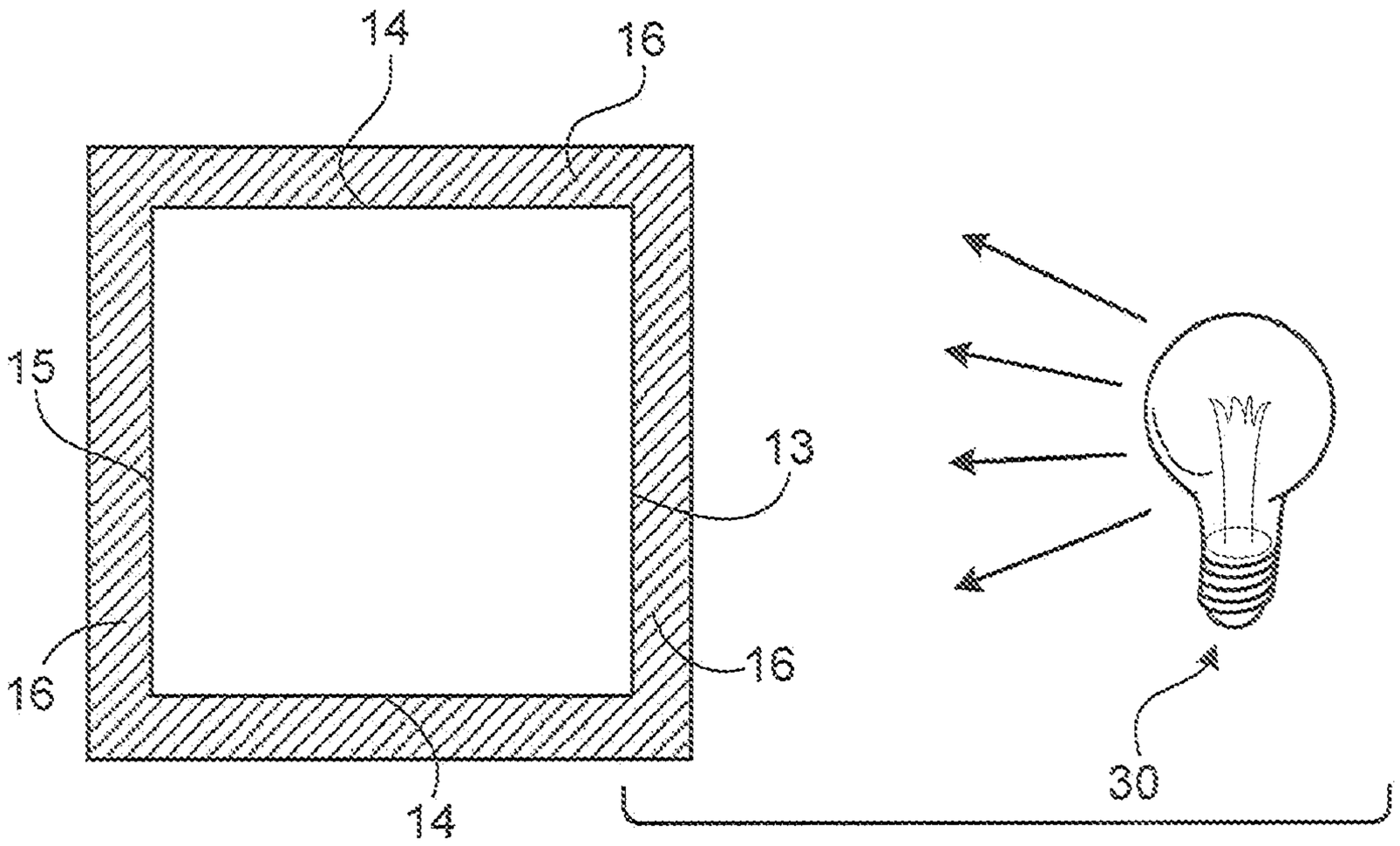


FIG. 3A

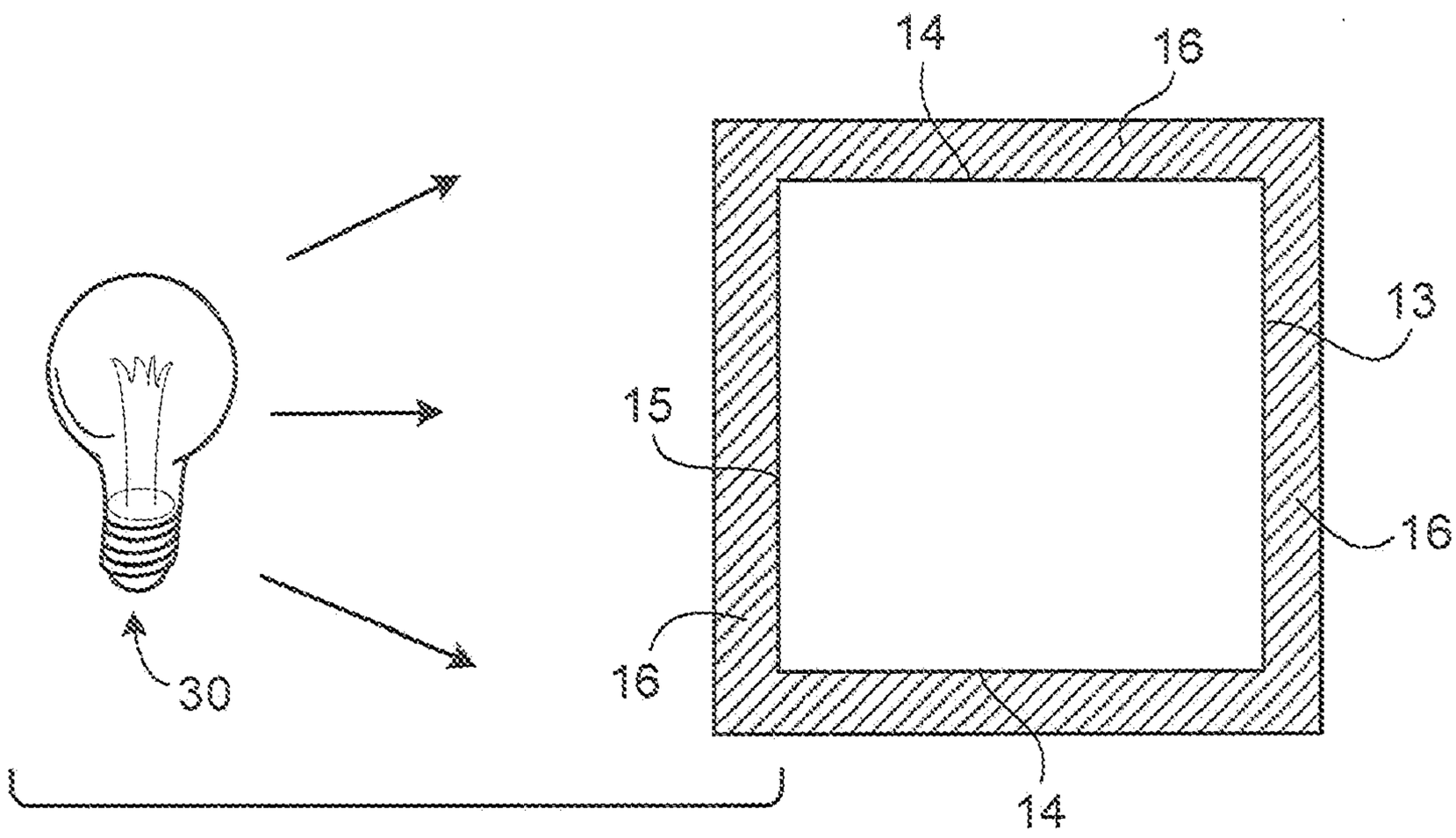


FIG. 3B

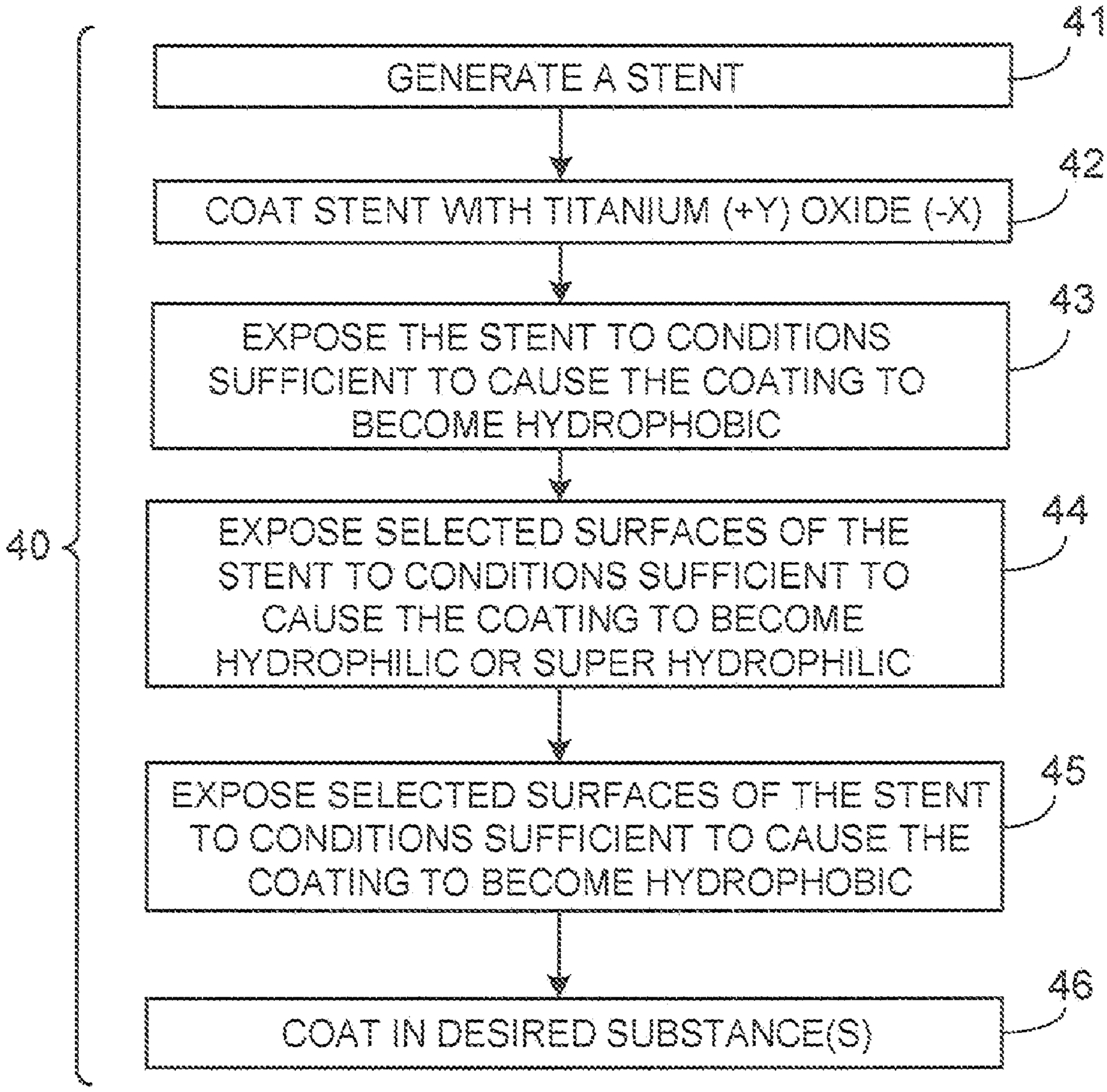

40
GENERATE A STENT
41
COAT STENT WITH TITANIUM (+Y) OXIDE (-X)
42
EXPOSE THE STENT TO CONDITIONS SUFFICIENT TO CAUSE THE COATING TO BECOME HYDROPHOBIC
43
EXPOSE SELECTED SURFACES OF THE STENT TO CONDITIONS SUFFICIENT TO CAUSE THE COATING TO BECOME HYDROPHILIC OR SUPER HYDROPHILIC
44
EXPOSE SELECTED SURFACES OF THE STENT TO CONDITIONS SUFFICIENT TO CAUSE THE COATING TO BECOME HYDROPHOBIC
45
COAT IN DESIRED SUBSTANCE(S)
46

FIG. 4

MEDICAL DEVICES WITH SELECTIVE COATING

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Ser. No. 60/818,101, filed on Jun. 29, 2006. The contents of U.S. Application Ser. No. 60/818,101 are incorporated by reference as part of this application.

TECHNICAL FIELD

[0002] This invention relates to medical devices, such as endoprostheses (e.g., stents).

BACKGROUND

[0003] The body defines various passageways such as arteries, other blood vessels, and other body lumens. These passageways sometimes become occluded or weakened. For example, the passageways can be occluded by a tumor, restricted by a plaque, or weakened by an aneurysm. When this occurs, the passageway can be reopened or reinforced, or even replaced, with a medical endoprosthesis. An endoprosthesis is typically a tubular member that is placed in a lumen in the body. Examples of endoprostheses include stents, covered stents, and stent-grafts.

[0004] Endoprostheses can be delivered inside the body by a catheter that supports the endoprosthesis in a compacted or reduced-size form as the endoprosthesis is transported to a desired site. Upon reaching the site, the endoprosthesis is expanded, for example, or allowed to expand, so that it can contact the walls of the lumen.

[0005] Endoprostheses can be coated with biocompatible materials and/or biomolecules, including active pharmaceutical agents.

SUMMARY

[0006] The disclosure relates to medical devices, such as endoprostheses. The invention is based, inter alia, on the discovery that coating endoprostheses, e.g., stents, with hydrophilic and/or hydrophobic material(s) allows for generation of complex biomolecule coating patterns on the endoprostheses.

[0007] In one aspect, the disclosure features a medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface and an outer abluminal wall surface and defining a central lumen or passageway, wherein the inner luminal wall surface and side wall surface of the bands and connectors forming transverse passageways through the elongated tubular structure bear a coating of hydrophilic material and the outer abluminal wall surface of the tubular structure bears a coating of hydrophobic material.

[0008] Embodiments may include one or more of the following features.

[0009] At least one or more selected regions of the luminal and side wall surfaces of the medical device can bear a coating of hydrophilic material, e.g., superhydrophilic material, or the entire luminal and side wall surfaces of the medical device can bear a coating of hydrophilic material, e.g., superhydrophilic material. At least one or more selected regions of the abluminal surface of the medical device can bear a coating of hydrophobic material or the entire abluminal wall surface of the medical device can bear a coating of hydrophobic material.

[0010] The coating of the luminal, side and abluminal wall surfaces can include titanium (+y) oxide (−x) (Ti_xO_y) e.g., titanium dioxide. Titanium (+y) oxide (−x) can have a crystalline structure, e.g., be in an anatase or rutile phase. Titanium (+y) oxide (−x) can be in an amorphous phase. Titanium (+y) oxide (−x) can be in an anatase phase combined with at least one of the following phases: rutile, brookite, monoclinic, amorphous, titanium (+y) oxide (−x) (II), and titanium (+y) oxide (−x) (H). Titanium (+y) oxide (−x) can be nano-porous, e.g., meso-porous or micro-porous. Titanium (+y) oxide (−x) can be generally smooth, i.e., not nano-porous. In addition to the titanium (+y) oxide (−x), the coating can include phosphorus, e.g., up to 5% of phosphorus by weight. In addition to the titanium (+y) oxide (−x) and/or phosphorus, the coating can include iridium oxide or ruthenium oxide or both. Titanium (+y) oxide (−x) can be doped with at least one of the following elements: iron, carbon, nitrogen, bismuth and vanadium, e.g., it can be doped with both bismuth and vanadium. A layer of organic compound, e.g., alkyl silane, aryl silane and/or fluoroalkyl silane, can be deposited over the titanium dioxide coating. Specific examples of organic compounds that can be deposited over the coating include octadecylsilane and octadecylphosphonic acid.

[0011] The coating upon the abluminal wall surface can also include biomolecules, e.g., paclitaxel, and a polymer, e.g., poly(styrene-b-isobutylene-b-styrene). The coating upon the abluminal wall surface can also include an organic solvent or a hydrophobic lipid capsule. The coating upon the abluminal wall surface, e.g., titanium (+y) oxide (−x) coating with biomolecules, e.g., titanium dioxide coating with biomolecules, can include a second layer of titanium (+y) oxide (−x), e.g., titanium dioxide.

[0012] The coating upon the luminal and side wall surfaces can also include biomolecules, e.g., heparin.

[0013] The coating upon the abluminal, luminal and side wall surfaces can include biomolecules. Biomolecules of the abluminal wall surface coating can be of a type different from biomolecules of the luminal and side wall surfaces coating.

[0014] In another aspect, the disclosure features a medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface and an outer abluminal wall surface and defining a central lumen or passageway, wherein the inner luminal wall surface and side wall surface of the bands and connectors forming transverse passageways through the elongated tubular structure bear a coating of hydrophobic material and the outer abluminal wall surface of the tubular structure bears a coating of hydrophilic material.

[0015] Embodiments may include one or more of the following features.

[0016] At least one or more selected regions of the luminal and side wall surfaces of the medical device can bear a coating of hydrophobic material or the entire luminal and side wall surfaces of the medical device can bear a coating of hydrophobic material. At least one or more selected regions of the abluminal surface of the medical device can bear a coating of hydrophilic material, e.g., superhydrophilic

material, or the entire abluminal wall surface of the medical device can bear a coating of hydrophilic material, e.g., superhydrophilic material.

[0017] The coating of the luminal, side and abluminal wall surfaces can include titanium (+y) oxide (−x), e.g., titanium dioxide. Titanium (+y) oxide (−x) can have a crystalline structure, e.g., be in an anatase or rutile phase. Titanium (+y) oxide (−x) can be in an amorphous phase. Titanium (+y) oxide (−x) can be in an anatase phase combined with at least one of the following phases: rutile, brookite, monoclinic, amorphous, titanium (+y) oxide (−x) (II), and titanium (+y) oxide (−x) (H). Titanium (+y) oxide (−x) can be nano-porous, e.g., meso-porous or micro-porous. Titanium (+y) oxide (−x) can be generally smooth, i.e., not nano-porous. In addition to the titanium (+y) oxide (−x), the coating can include phosphorus, e.g., up to 5% of phosphorus by weight. In addition to the titanium (+y) oxide (−x) and/or phosphorus, the coating can include iridium oxide or ruthenium oxide or both. Titanium (+y) oxide (−x) can be doped with at least one of the following elements: iron, carbon, nitrogen, bismuth and vanadium, e.g., it can be doped with both bismuth and vanadium. A layer of organic compound, e.g., alkyl silane, aryl silane and/or fluoroalkyl silane, can be deposited over the titanium (+y) oxide (−x) coating. Specific examples of organic compounds that can be deposited over the coating include octadecylsilane and octadecylphosphonic acid.

[0018] The coating upon the abluminal wall surface can also include biomolecules. The coating upon the abluminal wall surface, e.g., titanium (+y) oxide (−x) coating with biomolecules, e.g., titanium dioxide coating with biomolecules, can include a second layer of titanium (+y) oxide (−x), e.g., titanium dioxide.

[0019] The coating upon the luminal and side wall surfaces can also include biomolecules. The coating, e.g., including biomolecules, can also include a polymer, e.g., poly(styrene-b-isobutylene-b-styrene). The coating upon the luminal and side wall surfaces can also include an organic solvent or a hydrophobic lipid capsule. The coating upon the luminal and side wall surfaces, e.g., titanium (+y) oxide (−x) coating with biomolecules, e.g., titanium dioxide coating with biomolecules, can include a second layer of titanium (+y) oxide (−x), e.g., titanium dioxide.

[0020] The coating upon the abluminal, luminal and side wall surfaces can include biomolecules. Biomolecules of the abluminal wall surface coating can be of a different type than the biomolecules on the luminal and side wall surfaces coating.

[0021] In another aspect, the disclosure features a method of producing a medical device, the method having the following steps:

[0022] (i) coating wall surfaces of a medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface and an outer abluminal wall surface and defining a central lumen or passageway, wherein the inner luminal wall surface and side wall surface of the bands and connectors form transverse passageways through the elongated tubular structure with hydrophilic titanium (+y) oxide (−x), e.g., titanium dioxide;

[0023] (ii) exposing the medical device to conditions sufficient to cause the titanium (+y) oxide (−x) coating to become hydrophobic;

[0024] (iii) exposing selected surfaces of the medical device to conditions sufficient to cause the titanium (+y) oxide (−x) coating to become superhydrophilic; and

[0025] (iv) coating the medical device in a first solution compatible with desired biomolecules.

[0026] Embodiments may include one or more of the following features.

[0027] The first solution can be non-polar or polar. The first solution can include a desired biomolecule, e.g., paclitaxel or heparin. The first solution can also include a polymer, e.g., poly(styrene-b-isobutylene-b-styrene). The first solution can include a hydrophobic lipid capsule.

[0028] The first solution can include at least one polar solvent configured to adhere to the hydrophilic surfaces of the medical device and at least one non-polar solvent configured to adhere to the hydrophobic surfaces of the medical device. The solution can include at least one biomolecule compatible with at least one solvent, e.g., a first biomolecule compatible with the polar solvent and a second biomolecule compatible with the non-polar solvent. The first biomolecule can be heparin and the second biomolecule can be paclitaxel. The first solution can further comprise a polymer, e.g., poly(styrene-b-isobutylene-b-styrene). The first solution can include hydrophobic lipid capsules containing biomolecules, as well as hydrophilic groups.

[0029] The method can have a further step of coating the medical device in a second solution compatible with desired biomolecules. The second solution can be non-polar or polar. The second solution can include biomolecules, e.g., paclitaxel or heparin. The second solution can include a polymer. The second solution can include a hydrophobic lipid capsule.

[0030] The method can include a further step of coating the medical device of step (i) with a layer of organic compound, e.g., alkyl silane, aryl silane and/or fluoroalkyl silane, specifically, octadecylsilane or octadecylphosphonic acid.

[0031] The conditions of step (ii) can include placing the medical device in the dark and/or wet-rubbing. The conditions of step (iii) can include illuminating surfaces of the medical device that bear the coating with ultraviolet light. At least a region of the luminal and side wall surfaces that bear the coating can be illuminated. At least a region of the abluminal wall surface that bears the coating can be illuminated. Step (iii) can also include exposing at least a region of the surfaces that have become superhydrophilic to conditions sufficient for the surface region to become hydrophobic, e.g., by wet-rubbing or by placing the medical device in the dark.

[0032] The coating process of step (iv) can be dipcoating, gas-assisted spraying, electrostatic spraying, electrospinning and/or roll-coating.

[0033] The titanium (+y) oxide (−x) coating can be titanium dioxide coating. The coating can have a crystalline structure, e.g., be in a rutile or anatase phase. Titanium (+y) oxide (−x) can be in an amorphous phase. Titanium (+y) oxide (−x) can be in an anatase phase combined with at least one of the following phases: rutile, brookite, monoclinic, amorphous, titanium (+y) oxide (−x) (TI), and titanium (+y) oxide (−x) (H). Titanium (+y) oxide (−x) can be nano-porous, e.g., meso- or micro-porous. Titanium (+y) oxide (−x) can be generally smooth, i.e., not nano-porous. In addition to the titanium dioxide, the coating can include phosphorus, e.g., up to 5% of phosphorus by weight. In

addition to the titanium (+y) oxide (−x) and/or phosphorus, the coating can include iridium oxide or ruthenium oxide or both. Titanium (+y) oxide (−x) can be doped with at least one of the following elements: iron, carbon, nitrogen, bismuth and vanadium, e.g., it can be doped with both bismuth and vanadium. A layer of organic compound, e.g., alkyl silane, aryl silane and/or fluoroalkyl silane, can be deposited over the titanium (+y) oxide (−x) coating. Specific examples of organic compounds that can be deposited over the coating include octadecylsilane and octadecylphosphonic acid.

[0034] The instant disclosure provides stents with various patterns of hydrophobic and hydrophilic coating. These coating patterns allow placement of various biomolecules on various regions of a stent resulting in complex biomolecule patterns on stents. The disclosure also provides methods of generating stents with such complex coating and/or biomolecule patterns.

[0035] The term "biomolecule" as used herein refers to chemical compounds, therapeutic agents, drugs, pharmaceutical compositions and similar substances that exert biological effects.

[0036] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. Other features and advantages of the disclosure will be apparent from the following detailed description, and from the claims.

DESCRIPTION OF DRAWINGS

[0037] FIG. **1**A is a perspective view of a stent.

[0038] FIG **1**B is a cross-section of a wall of the stent taken along the lines A1-A1.

[0039] FIG. **2** is a flow chart of an embodiment of a method of selectively coating the stent.

[0040] FIG. **3**A is a cross-section of a wall of the stent of FIG IA, taken along the lines A1-A1.

[0041] FIG. **3**B is a cross-section of a wall of the stent of FIG IA, taken along the lines A1-A1.

[0042] FIG. **4** is a flow chart of another embodiment of a method of selectively coating the stent.

DETAILED DESCRIPTION

[0043] Referring to FIG IA, stent **10** having a body of interconnected bands **12** and connectors **11** forming an elongated tubular structure is shown. Referring to FIG. **1**B, the cross-section of the body of stent **10** shows that the stent has an inner luminal surface **13**, side wall surface **14** and an outer abluminal surface **15**. The surfaces **13**, **14** and **15** bear a coating **16** of titanium (+y) oxide (−x) (Ti_xO_y) e.g., titanium dioxide (TiO_2). Coating **16** of luminal surface **13** and side wall surface **14** further includes biomolecules **17**. Coating **16** of abluminal surface **15** further includes biomolecules **18**.

[0044] Stent **10** can be produced in a variety of ways. For example, referring to FIG. **2**, a method **20** of producing stent **10** with selectively coated surfaces is described. Stent **10** is generated (step **21**). Surfaces **13**, **14** and **15** of stent **10** are coated with Ti_xO_y (step **22**), e.g., hydrophilic Ti_xO_y, e.g., superhydrophilic Ti_xO_y, e.g., superhydrophilic TiO_2, resulting in coating **16**. Stent **10** is then be exposed to conditions sufficient to cause the Ti_xO_y coating **16** to become hydrophobic (step **23**), e.g., by placing stent **10** in a dark environment for a couple of days or by a process called "wet-rubbing" (see, e.g., Kamei et al., *Surf. Science* 463:L609-12, 2000), in which a superhydrophilic surface is turned to a hydrophobic surface by removal of the surface hydroxyl groups.

[0045] Selected surfaces of stent **10** are then exposed to conditions sufficient to cause coating **16** of the selected surfaces to become hydrophilic, e.g., superhydrophilic (step **24**), e.g., by exposure to ultraviolet light. For example, referring to FIG. **3**A, a source of ultraviolet light **30** can be placed generally on the luminal side of stent **10**, e.g., inside stent **10**. Light source **30** illuminates luminal surface **13** and side wall surface **14** bearing Ti_xO_y coating **16**. Such illumination will cause coating **16** to become superhydrophilic. While light source **30** illuminates surfaces **13** and **14**, abluminal surface **15** bearing coating **16** is blocked from exposure, e.g., with a mandrel. Thus, after sufficient illumination, the resulting stent **10** bears coating **16** that is superhydrophilic on luminal surface **13** and side walls surface **14**, and hydrophobic on abluminal surface **15**.

[0046] In another embodiment, illustrated in FIG. **3**B, a source of ultraviolet light **30** can be placed generally on the abluminal side of stent **10**. Light source **30** illuminates the abluminal surface **15** that bears coating **16** of Ti_xO_y. While light source **30** illuminates surface **15**, surfaces **13** and **14** are blocked. Thus, after sufficient illumination, the resulting stent **10** bears coating **16** that is hydrophilic on abluminal surface **15** and hydrophobic on luminal surface **13** and side surface **14**.

[0047] Both the light exposure, e.g., ultraviolet light exposure, and wet-rubbing can be carried out on a selective micro-scale, vastly expanding the range of hydrophilic and hydrophobic regions of stent **10** that can be realized. Other patterns, in addition to the ones described above can be realized. For example, coating **16** of both luminal surface **13** and abluminal surface **15** can be turned hydrophilic with selective light exposure. In another example, only portions of coating **16** of any of the surfaces **13**, **14** and/or **15** may be turned hydrophilic. The possible patterns are numerous.

[0048] Further referring to FIG. **2**, stent **10** bearing coating **16** that is selectively hydrophilic and hydrophobic is then coated, e.g., by dipcoating, gas-assisted spraying, electrostatic spraying, electrospinning, or roll-coating, in desired substances compatible with desired biomolecules **17** and **18** (step **25**). For example, stent **10** can be coated, e.g., dipped in a non-polar solution containing a biomolecule, e.g., paclitaxel in Xylene (e.g., up to 1% by weight of paclitaxel) and optionally a polymer, e.g., poly(styrene-b-isobutylene-b-styrene) (SIBS). Non-polar solution and biomolecule adhere to non-illuminated surfaces bearing hydrophobic coating **16**. The stent can be dried and the process repeated, building layers upon the hydrophobic surfaces. In another embodiment, stent **10** can be further coated, e.g., dipped in a polar solution containing another biomolecule, e.g., heparin. The polar solution will adhere to illuminated surfaces

bearing hydrophilic coating **16**. In yet another embodiment, stent **10** can be coated, e.g., by dipcoating, gas-assisted spraying, electrostatic spraying, electrospinning, or roll coating, in a solution that includes a combination of both polar and non-polar solvents with respectively dissolved biomolecules and, optionally, polymers. In this embodiment, the polar solvent will adhere to the hydrophilic regions of stent **10**, while the non-polar solvent will adhere to the hydrophobic regions of stent **10**. The resulting stent **10** will have surfaces selectively coated with multiple biomolecules.

[0049] Thus, in one embodiment, stent **10** bears coating **16** of hydrophilic Ti_xO_y. Stent **10** is left in the dark for a time sufficient for coating **16** to become hydrophobic. Next, luminal surface **13** and side wall surface **14** are illuminated with UV light source **30**, turning them superhydrophilic. Such luminal surface **13** and side wall surface **14** bearing hydrophilic coating **16** are coated with polar solutions and biomolecules, e.g., heparin. The abluminal wall surface **15** bearing hydrophobic coating **16**, on the other hand, is coated with non-polar solutions and biomolecules, e.g., paclitaxel, e.g., paclitaxel and binder polymer, e.g., SIBS. In one embodiment, stent **10** can be coated with a solution that includes a combination of both polar and non-polar solvents with respectively dissolved biomolecules and, optionally, polymers.

[0050] In another embodiment, stent **10** bears coating **16** of hydrophilic Ti_xO_y. Stent **10** is left in the dark for a time sufficient for it to become hydrophobic. Next, abluminal wall surface **15** bearing coating **16** is illuminated with UV light source **30**, turning it superhydrophilic. Luminal surface **13** and side wall surface **14** bearing coating **16** are coated with non-polar solutions and biomolecules. The abluminal surface **15** is coated with polar solutions and biomolecules. In one embodiment, stent **10** can be coated with a solution that includes a combination of both polar and non-polar solvents with respectively dissolved drugs and, optionally, polymers.

[0051] As discussed supra, in another embodiment, rather than illuminating the entire luminal surface **13** and side wall surface **14** bearing coating **16** or the entire abluminal surface **15** (in step **24** of FIG. **2**), selected regions of any of surfaces **13**, **14** and **15** may be illuminated, and selected regions may be coated in desired polar and non-polar solutions. Any number and variation of coating patterns is possible.

[0052] Referring to FIG. **4**, another method of generating a selectively coated stent **10** is illustrated. Stent **10** is generated (step **41**). Surfaces **13**, **14** and **15** of stent **10** are coated with Ti_xO_y (step **42**), e.g., hydrophilic Ti_xO_y, e.g., superhydrophilic Ti_xO_y, e.g., superhydrophilic TiO_2, resulting in coating **16**. Stent **10** is then exposed to conditions sufficient to cause the Ti_xO_y coating **16** to become hydrophobic (step **43**), e.g., by placing stent **10** in a dark environment for a few days. Surfaces **13**, **14** and/or **15** or selected portions of surfaces **13**, **14** and **15** of stent **10** bearing coating **16** are then exposed to conditions sufficient to cause the coating **16** to become hydrophilic, e.g., superhydrophilic, e.g., by UV illumination (e.g., XE lamp, 20 minutes exposure time) (step **44**). Selected surfaces exposed to UV illumination can include the entire surfaces **13**, **14** and **15** bearing coating **16**. Selected surfaces that have been exposed to UV illumination are subsequently exposed to conditions sufficient to cause coating **16** to become hydrophobic (step **45**). The conditions can include wet-rubbing selected surfaces, e.g., luminal and abluminal surfaces, or any other combination of surfaces, with either a glass, a steel or a paper surface (see, e.g., Kamei et al.). Again, both the wet-rubbing and the UV exposure can be done on a selective micro-scale, vastly expanding the range of patterns of hydrophobic and hydrophilic regions that can be realized.

[0053] Further referring to FIG. **4**, stent **10** is coated, e.g., by dipcoating, gas-assisted spraying, electrostatic spraying, electrospinning or roll-coating, in desired substance(s) (step **46**). One interesting application of wet-rubbing is that it allows just the surface to be turned from a hydrophilic porous Ti_xO_y coating into a hydrophobic surface, while leaving the buried (underlying) porous structure hydrophilic. This can enable coating stent **10** with various combinations of polar and non-polar solvents with different dissolved drugs and/or polymers to create contrasting coating composition from top to bottom inside of the porous Ti_xO_y coating. In one embodiment, stent **10** can be coated, e.g., by dipcoating, gas-assisted spraying, electrostatic spraying, electrospinning or roll-coating, in a non-polar solution containing biomolecules, e.g., paclitaxel, e.g., paclitaxel and binder polymer, e.g., SIBS, and in a polar solution containing biomolecules, e.g., heparin, e.g., heparin and polymer. In another embodiment, stent **10** can be coated, e.g., by dipcoating, gas-assisted spraying, electrostatic spraying, electrospinning or roll-coating, in a solution that includes a combination of both polar and non-polar solvents with respectively dissolved biomolecules, e.g., drugs, and, optionally, polymers.

[0054] In another embodiment, once stent **10** has been coated with desired biomolecules and/or polymers, a second porous coating of Ti_xO_y can be applied. In this embodiment, Ti_xO_y can be applied without the use of high-temperature step. Ti_xO_y can be applied, e.g., via microwave-assisted deposition. In this embodiment, biomolecules on the stent, e.g., paclitaxel, can diffuse through the pores of the second Ti_xO_y layer.

[0055] In another embodiment, hydrophilic biomolecules can be packaged into hydrophobic lipid capsules (e.g., liposomes) and applied to hydrophobic coating **16**.

[0056] Further referring to FIG. **4**, step **42** of method **40** can include coating selected regions stent **10** with Ti_xO_y that is nano-porous, e.g., meso-porous or micro-porous, and other selected regions with Ti_xO_y that is generally smooth, i.e., not nano-porous. In one embodiment, the regions coated with nano-porous coating can be luminal and side wall surfaces **13** and **14**, while the regions with smooth coating can be abluminal wall surfaces **15**. In another embodiment, the regions with nano-porous coating can be abluminal wall surfaces **15**, while the regions with smooth coating can be luminal and side wall surfaces **13** and **14**. Entire stent **10** coated with nano-porous and smooth Ti_xO_y can then be exposed to conditions sufficient for coating **16** to become superhydrophilic, e.g., by UV irradiation (step **44**). Entire stent **10** can then be exposed to conditions sufficient to cause selected regions of coating **16** to become hydrophobic, e.g., by placing stent **10** in dark conditions for a certain timeframe, e.g., a number of days or weeks (step **45**). In step **45**, the regions coated with nano-porous Ti_xO_y will remain superhydrophilic (see, e.g., Gu, *App. Phys. Lett.* 85(21): 5067-69, 2004), while the regions coated with smooth Ti_xO_y will become hydrophobic. The resulting stent **10** can be coated e.g., by dipcoating, gas-assisted spraying, electrostatic spraying, electrospinning or roll-coating, in desired substance(s) (step **46**). Stent **10** can be coated with polar

solutions, non-polar solutions or solutions containing a combination of polar and non-polar solvents, containing compatible biomolecules and/or polymers, as discussed above.

[0057] In use, stent **10** can be used, e.g., delivered, using a catheter delivery system. Catheter systems are described, e.g., in Wang U.S. Pat. No. 5,195,969, Hamlin U.S. Pat. No. 5,270,086, and Raeder-Devens U.S. Pat. No. 6,726,712. Stents and stent delivery are also exemplified by the Radius® or Symbiot® systems, available from Boston Scientific Scimed, Maple Grove, Minn. Stent **10** bearing more than one type of a biomolecule, e.g., biomolecules **17** and **18**, can deliver the biomolecules to, e.g., a blood vessel. Biomolecules **17** and **18** can target various cells of the blood vessels, e.g., endothelial cells or smooth muscle cells.

[0058] As discussed, coating **16** of stent **10** can include Ti_xO_y, preferably, titanium dioxide. Titanium dioxide, also known as titanium (IV) oxide or titania is the naturally occurring oxide of titanium, chemical formula TiO_2. TiO_2occurs in a number of forms: rutile, anatase, brookite, titanium dioxide (B) (monoclinic), titanium dioxide (II), and titanium dioxide (H). Carp et al., *Prog. Solid State Chem.* 32:33-177, 2004. TiO_2 coatings are known to be blood-compatible. Maitz et al., Boston Scientific Corporation internal report, 2001; Tsyganov et al., *Surf. Coat. Tech.* 200:1041-44, 2005. Blood-compatible substances show only minor induction of blood clot formation. TiO_2 in both rutile and anatase phases shows low platelet adhesion. Implantation of phosphorus in the top surface of the rutile phase (e.g., at an ion density of about 2% to about 5%) decreases platelet adhesion to TiO_2. Maitz et al.

[0059] Morphology, crystal structure and doping of Ti_xO_y coating **16** are some elements that need to be taken into account when making and using stent **10**. Ti_xO_y coating **16** of stent **10** can be a crystal (anatase or rutile structure). Crystal structure is photoactive. Crystal structure also has porosity or roughness that facilitates adhesion and storage of biomolecules **17** and **18**, that can be placed on coating **16** alone or in combination with polymers and/or other biomolecules. Coating **16** can also be amorphous (Karuppuchamy et al., *Vacuum* 80:494-98, 2006) or be a combination of one or more of the following phases: anatase, rutile, brookite, amorphous, monoclinic, titanium (+y) oxide (−x) (II) and/or titanium (+y) oxide (−x) (H).

[0060] Instead of using pure Ti_xO_y for coating, phosphorus can be embedded at a low percentage (e.g., about 0.5 to about 5%) into the Ti_xO_y layer (e.g., using plasma immersion process) to increase blood compatibility of the coating. Maitz et al.

[0061] In other embodiments, coating **16** can be a combination of Ti_xO_y and iridium oxide (IrOx); or a combination of Ti_xO_y and ruthenium oxide (RuOx); or a combination of Ti_xO_y, IrOx and RuOx. RuOx and IrOx can decrease any potential inflammation ongoing in the cells surrounding stent **10** in the body, because these compounds can catalyze breakdown of by-products of stressed cells.

[0062] In one embodiment, Ti_xO_y coating **16** can be doped, e.g., with iron (Fe), carbon (C), nitrogen (N), bismuth (Bi), vanadium (V) or their combination. Fe-doping enhances Ti_xO_y conversion rate of photoinduced hydrophilicity and reduces the rate of conversion from hydrophilic to hydrophobic state. Yu et al., *Mat. Chem. Phys.* 95:193-96, 2006. Bi- and/or V-doping can decrease the water contact angle, while Bi—V-doping can enhance maintenance of a low water contact angle under dark conditions. Hong et al., *Mat. Lett.* 60:1296-1305, 2006. C-doping has also been reported to influence hydrophilic properties of TiO_2. Irie et al, *Thin Solid Films* 510:21-5, 2006.

[0063] A number of techniques can be used to deposit Ti_xO_y coating **16** on stent **10**, including sol-gel routes and cathodic electrodeposition. Karuppuchamy et al., *Solid State Ionics* 151:19-27, 2002; Karuppuchamy et al., *Mat. Chem. Phys.* 93:251-54, 2005; Hattori et al., *Langmuir* 15:5422-25, 1999. Many deposition techniques utilize a high-temperature processing step (e.g., heating to about 400° C.) to turn deposited film into crystal structure. If such a high-temperature step is undesirable (e.g., if the stent already has a coating of thermo-sensitive elements, such as certain polymers, microelectromechanical systems (MEMs), or biomolecules), microwave-assisted deposition of Ti_xO_y can be used. Vigil et al., *Langmuir* 17:891-96, 2001, Gressel-Michel et al., *J. Coll. Interf. Science* 285:674-79, 2005. In one method of microwave-assisted deposition, anatase particles are synthesized directly in suspension using a microwave reactor and the particles (of about 70 nm in diameter) are deposited by a dipcoat process at room temperature. Gressel-Michel et al. Chemical bath deposition is another method that avoids a high-temperature step in Ti_xO_y deposition. Pathan et al., *App. Surf. Science* 246:72-76, 2005.

[0064] As mentioned above, hydrophilic Ti_xO_y coating **16** will turn hydrophobic when left in the dark. Yu et al.; Karuppuchamy et al., 2005. Ti_xO_y coatings, however, are known to switch from hydrophobic to superhydrophilic when exposed to ultraviolet (UV) light illumination. This effect exists not only in the anatase and rutile phases (Yu et al.), but also in the amorphous phase (Karuppuchamy et al, *Vacuum* 80:494-98, 2006). Ti_xO_y is also a photocatalyst under UV light, but the photocatalytic effect only exists in the anatase phase. A superhydrophilic surface can contact water with an angle of less than 5°. The superhydrophilic effect of Ti_xO_y is larger for nano-porous structure, e.g., meso-porous structure (that with pore diameters between 20 and 500 angstroms) due to the enlarged surface area (Yu et al., *J. Photochem. Photobiol. A,* 148:331-39, 2002) and micro-porous structure. Thus, exposure of hydrophobic Ti_xO_y coating **16** to UV light source **30** (e.g., 365 nm, 5 $mWcm^{-2}$) will switch the material back to superhydrophilic.

[0065] The source of UV light **30** for illuminating stent **10** bearing Ti_xO_y coating **16** can be, e.g., fibers coupled to high-power diode lasers. The fibers can be fitted with diffusers that allow sideways radiation. When fibers or plastic rods or sheets are notched, light is reflected out from the opposite side of the material. Light uniformity is achieved by increasing the notch depth and frequency, as the distance from the light source increases. Rotating this fiber inside stent **10** can provide uniform illumination in all directions. Instead of rotating the fiber, a threaded notch can be generated that will illuminate all directions without the need for rotation. Fibers can be obtained from, e.g., polyMicro (www.polymicro.com). Silica fibers offer good UV transmission. The fibers can be, e.g., about 600 μm to about 2 mm in diameter.

[0066] As discussed, placing stent **10** coated with hydrophilic, e.g., superhydrophilic, Ti_xO_y, e.g., superhydrophilic TiO_2, in the dark will turn Ti_xO_y coating **16** hydrophobic. In some embodiments, however, it may be desirable to store (e.g., in the dark, e.g., in packaging) stents coated with hydrophilic, e.g., superhydrophilic Ti_xO_y, without its turning

hydrophobic. Reversal from superhydrophilic to hydrophobic surface can be prevented by using a nano-porous (inverse-opal) structure of Ti_xO_y Gu, *App. Phys. Lett.* 85(21): 5067-69, 2004.

[0067] In one embodiment, a layer of organic compound, e.g., alkyl silane, aryl silane and/or fluoroalkyl silane, can be deposited over the hydrophobic Ti_xO_y. For example, a layer of octadecylsilane or octadecylphosphonic acid over the hydrophobic Ti_xO_y coating **16** can enhance the superhydrophobic state and stability of coating **16**. Balaur et al., *Electrochem. Communic.* 7:1066-70, 2005. Coating **16** in this embodiment can be turned hydrophilic, e.g., superhydrophilic, by UV light illumination, as desired.

[0068] Stent **10** can include (e.g., be manufactured from) metallic materials, such as stainless steel (e.g., 316L, Bio-Dur® 108 (UNS S29108), and 304L stainless steel, and an alloy including stainless steel and 5-60% by weight of one or more radiopaque elements (e.g., Pt, Ir, Au, W) (PERSS®) as described in US-2003-0018380-A1, US-2002-0144757-A1, and US-2003-0077200-A1), Nitinol (a nickel-titanium alloy), cobalt alloys such as Elgiloy, L605 alloys, MP35N, titanium, titanium alloys (e.g., Ti-6Al-4V, Ti-50Ta, Ti-10Ir), platinum, platinum alloys, niobium, niobium alloys (e.g., Nb-1Zr) Co-28Cr-6Mo, tantalum, and tantalum alloys. Other examples of materials are described in commonly assigned U.S. application Ser. No. 10/672,891, filed Sep. 26, 2003; and U.S. application Ser. No. 11/035,316, filed Jan. 3, 2005. Other materials include elastic biocompatible metal such as a superelastic or pseudo-elastic metal alloy, as described, for example, in Schetsky, L. McDonald, "Shape Memory Alloys", Encyclopedia of Chemical Technology (3rd ed.), John Wiley & Sons, 1982, vol. 20. pp. 726-736; and commonly assigned U.S. application Ser. No. 10/346,487, filed Jan. 17, 2003.

[0069] In some embodiments, materials for manufacturing stent **10** include one or more materials that enhance visibility by MRI. Examples of MRI materials include non-ferrous metals (e.g., copper, silver, platinum, or gold) and non-ferrous metal-alloys containing superparamagnetic elements (e.g., dysprosium or gadolinium) such as terbium-dysprosium, dysprosium, and gadolinium. Alternatively or additionally, stent **10** can include one or more materials having low magnetic susceptibility to reduce magnetic susceptibility artifacts, which during imaging can interfere with imaging of tissue, e.g., adjacent to and/or surrounding the stent. Low magnetic susceptibility materials include those described above, such as tantalum, platinum, titanium, niobium, copper, and alloys containing these elements.

[0070] Stent **10** can be of a desired shape and size (e.g., coronary stents, aortic stents, peripheral vascular stents, gastrointestinal stents, urology stents, and neurology stents). Depending on the application, stent **10** can have a diameter of between, e.g., about 1 mm to about 46 mm. In certain embodiments, a coronary stent can have an expanded diameter of from about 2 mm to about 6 mm. In some embodiments, a peripheral stent can have an expanded diameter of from about 5 mm to about 24 mm. In certain embodiments, a gastrointestinal and/or urology stent can have an expanded diameter of from about 6 mm to about 30 mm. In some embodiments, a neurology stent can have an expanded diameter of from about 1 mm to about 12 mm. An abdominal aortic aneurysm (AAA) stent and a thoracic aortic aneurysm (TAA) stent can have a diameter from about 20 mm to about 46 mm. Stent **10** can be balloon-expandable, self-expandable, or a combination of both (e.g., U.S. Pat. No. 5,366,504).

[0071] Stent **10** can include a releasable biomolecule, e.g., a therapeutic agent, drug, or a pharmaceutically active compound, such as described in U.S. Pat. No. 5,674,242, U.S. application Ser. No. 09/895,415, filed Jul. 2, 2001, and U.S. application Ser. No. 10/232,265, filed Aug. 30, 2002. The therapeutic agents, drugs, or pharmaceutically active compounds can include, for example, anti-proliferative agents, anti-thrombogenic agents, antioxidants, anti-inflammatory agents, immunosuppressive compounds, anesthetic agents, anti-coagulants, and antibiotics. Specific examples of such biomolecules include paclitaxel, sirolimus, everolimus, zotarolimus, picrolimus and dexamethasone.

[0072] A number of embodiments have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the disclosure. Accordingly, other embodiments are within the scope of the following claims.

What is claimed is:

1. A medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface and an outer abluminal wall surface and defining a central lumen or passageway, wherein said inner luminal wall surface and side wall surface of the bands and connectors forming transverse passageways through the elongated tubular structure bear a coating of hydrophilic material and said outer abluminal wall surface of the tubular structure bears a coating of hydrophobic material.

2. The medical device of claim **1**, wherein at least one or more selected regions of the luminal and side wall surfaces bears a coating of hydrophilic material.

3. The medical device of claim **2**, wherein the material is superhydrophilic.

4. The medical device of claim **1**, wherein at least one or more selected regions of the abluminal wall surface bears a coating of hydrophobic material.

5. The medical device of claim **1**, wherein the coating of the luminal, side and abluminal wall surfaces comprises titanium (+y) oxide (−x).

6. The medical device of claim **5**, wherein the coating further comprises a layer of organic compound over titanium (+y) oxide (−x).

7. The medical device of claim **5**, wherein the coating upon the abluminal wall surface further comprises a biomolecule.

8. The medical device of claim **7**, wherein the coating further comprises a polymer.

9. The medical device of claim **5**, wherein the coating upon the luminal and side wall surfaces further comprises a biomolecule.

10. A medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface and an outer abluminal wall surface and defining a central lumen or passageway, wherein said inner luminal wall surface and side wall surface of the bands and connectors forming transverse passageways through the elongated tubular structure bear a coating of hydrophobic material and said outer abluminal wall surface of the tubular structure bears a coating of hydrophilic material.

11. The medical device of claim **10**, wherein at least one or more selected regions of the luminal and side wall surfaces bears a coating of hydrophobic material.

12. The medical device of claim **10**, wherein at least one or more selected regions of the abluminal wall surface bears a coating of hydrophilic material.

13. The medical device of claim **12**, wherein the material is superhydrophilic.

14. The medical device of claim **10**, wherein the coating of the luminal, side and abluminal wall surface comprises titanium (+y) oxide (−x).

15. The medical device of claim **14**, wherein the coating further comprises a layer of organic compound over titanium (+y) oxide (−x).

16. The medical device of claim **14**, wherein the coating upon the abluminal wall surface further comprises a biomolecule.

17. The medical device of claim **14**, wherein the coating upon the luminal and side wall surfaces further comprises a biomolecule.

18. The medical device of claim **17**, wherein the coating further comprises a polymer.

19. A method of producing a medical device, the method comprising:

(i) coating wall surfaces of a medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface and an outer abluminal wall surface and defining a central lumen or passageway, wherein said inner luminal wall surface and side wall surface of the bands and connectors form transverse passageways through the elongated tubular structure with hydrophilic titanium (+y) oxide (−x);

(ii) exposing the medical device to conditions sufficient to cause the titanium (+y) oxide (−x) coating to become hydrophobic;

(iii) exposing selected surfaces of the medical device to conditions sufficient to cause the titanium (+y) oxide (−x) coating to become superhydrophilic; and

(iv) coating the medical device in a first solution compatible with desired biomolecules.

20. The method of claim **19**, wherein the first solution comprises at least one polar solvent configured to adhere to hydrophilic surfaces of the medical device and at least one non-polar solvent configured to adhere to the hydrophobic surfaces of the medical device.

21. The method of claim **20**, wherein the solution further comprises at least one biomolecule compatible with at least one solvent.

22. The method of claim **21**, wherein the solution further comprises a polymer.

23. The method of claim **19**, further comprising coating the medical device in a second solution compatible with desired biomolecules.

24. The method of claim **23**, wherein the second solution is non-polar.

25. The method of claim **23**, wherein the second solution is polar.

26. The method of claim **23**, wherein the second solution comprises a desired biomolecule.

27. The method of claim **26**, wherein the second solution comprises a polymer.

28. The method of claim **19**, further comprising coating the medical device of step (i) with a layer of organic compound.

29. The method of claim **19**, wherein the conditions of step (ii) comprise placing the medical device in a dark environment.

30. The method of claim **19**, wherein the conditions of step (iii) comprise illuminating the surfaces of the medical device that bear the titanium (+y) oxide (−x) coating with ultraviolet light.

31. The method of claim **30**, wherein at least a region of the luminal and side wall surfaces that bear the coating is illuminated.

32. The method of claim **30**, wherein at least a region of the abluminal wall surface that bears the coating is illuminated.

33. The method of claim **30**, wherein step (iii) further comprises exposing at least a region of surfaces that have become superhydrophilic to conditions sufficient for the region to become hydrophobic.

* * * * *